REMARKS

Claims 1, 2, 4-14, 16-27, 29-38, and 51-53 are pending in the present application. By virtue of this response, claims 1, 2, 8, 9, 13, 14, 20, 21, 26, 27, 33, 34 have been amended in accordance with the Examiner's suggestions (discussed in more detail below), and claim 31 has been amended to correct the dependency. No new matter has been added.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Applicants acknowledge with thanks the Examiner's withdrawal of the §102(b), §102(e) and §103(a) rejections set forth at paragraphs 10-12 of the previous Office Action, and the Examiner's willingness to hold in abeyance the obviousness-type rejections over co-pending application numbers 11/194,989 and 11/195,207 until all other rejections are resolved.

Objections to the Specification

The Examiner objects, as set forth at page 4 of the pending Office Action, to the phrase "a monoclonal antibody comprising amino acid sequence of SEQ ID NO:4 and 6" in claims 8, 9, 20, 21, 33 and 34, as awkward. In accordance with the Examiner's suggestion, this phrase has been amended to read "a monoclonal antibody comprising the amino acid sequences of SEQ ID NOs:4 and 6." Applicants respectfully request that this objection be withdrawn.

Obviousness-Type Double Patenting

Claims 1, 2, 10, 13, 14, 22, 26, 27, and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 41-43 of copending Application No. 11/413,817.

Applicants respectfully request that this rejection be held in abeyance until the Patent Office has made a determination of allowable claims in the present application or in co-pending Application No. 11/413,817, at which time Applicants will address this issue.

Rejections Under 35 USC §112, 1st paragraph

Claims 1-12 and 51 stand rejected under 35 USC §112, 1st paragraph. The Examiner alleges at page 6 of the present Office Action that the specification, while enabling for a method of administering an effective amount of a pharmaceutical composition comprising an antibody that binds specifically to amino acids 28-40 of $Aß_{1-40}$ peptide and a pharmaceutically acceptable carrier to a subject in need of reduction of brain amyloid plaques, wherein the antibody does not show significant cross-reactivity with $Aß_{1-42}$ and $Aß_{1-43}$ peptide, and wherein said administration results in reduction of amyloid plaques in the brain of said subject, does not reasonably provide enablement for a method of treating Alzheimer's disease as broadly claimed. The Examiner further states that the specification does not enable any person skilled in the part to which it pertains to practice the invention commensurate with these claims.

Applicants respectfully traverse this rejection, in view of the arguments presented below.

The specification states at paragraph [0065] that

> [a]s used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For purposes of this invention, ***beneficial or desired clinical results include***, but are not limited to, ***one or more of the following***: inhibiting or suppressing the formation of amyloid plaques, ***reducing***, removing, or clearing ***amyloid plaques***, improving cognition or reversing cognitive decline, sequestering soluble Aß peptide circulating in biological fluids, reducing Aß peptide (including soluble and deposited) in a tissue (such as brain), inhibiting and/or reducing accumulation of Aß peptide in the brain, inhibiting and/or reducing toxic effects of Aß peptide in a tissue (such as brain), decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of patients (emphasis added).

Thus the term "method of treating" as used in the present claims encompasses any approach for obtaining *any one or more* of the beneficial or desired clinical results listed above, including, e.g. reduction of brain amyloid plaques, which the Examiner has acknowledged is enabled. There is nothing in the definition of "treating" used by

Applicants (or any other commonly accepted definition of the term) that requires each and every aspect of Alzheimer's disease to be addressed by a given therapy in order for the therapy to be considered a "treatment" for, or "method of treating," Alzheimer's disease.

The Examiner further asserts at page 8 of the Office Action that "Applicant fails to provide guidance on the treatment of these other features [i.e. short-term memory loss, behavioral abnormalities, changes in permeability of the blood brain barrier, vascular damage] associated with Alzheimer's disease pathology, which would be encompassed by treatment of AD." The Examiner does not, and cannot, provide a legal or scientific basis for this requirement that these other "features" would *necessarily* be encompassed by treatment of Alzheimer's disease and therefore *must* be addressed for claims directed to a method of treating Alzheimer's disease to be enabled; no such basis exists.

The Examiner goes on to say that "the animal model used in the instant specification is not recognized as providing for teachings that are predictive of the results that would be effective for the full scope of the claims" (Office Action at 9), citing Münch & Robinson, *J Neural Transm* (2002) 109:1081-1087 (hereinafter "Münch"). But Münch does not state that transgenic mouse models of Alzheimer's disease are not predictive of the clinical results of immunization of humans with anti-Aß antibodies for the treatment of Alzheimer's disease. Münch only discusses transgenic mouse models in the context of active immunization (i.e. with Aß peptide), rather than passive immunization (i.e. with anti-Aß antibodies) as in the presently claimed invention. Even in the active immunization context, Münch does not critique the ability of transgenic mouse models to predict the *therapeutic* effect of immunization, but rather points out their inability to adequately predict the potential neuroinflammatory response in active immunization of humans, such as that which occurred in the phase 2A trials of Elan and Wyeth's AN-1792 Aß peptide vaccine:

> These [transgenic] mice develop Aß plaques and associated memory impairment; vaccination with human Aß causes antibodies to target the plaques, which are then removed by phagocytes and memory is restored. There is however, an important difference between these mice and humans. The antibody response in mice is elicited against the human form of Aß, which has an amino acid sequence that is different from the mouse form. This allows the production of high titer antibodies against

> the non-functional human Aß, while limiting the humoral- and cell-mediated response against the endogenous mouse Aß sequence. Therefore, the autoimmune response in mice is less likely to run the risk of incurring collateral damage by targeting functionally important APP and soluble Aß.

Münch at 1083; internal citations omitted.

After acknowledging "that passive immunization with anti-Aß antibodies leads to beneficial results in animal models of Alzheimer's disease," the Examiner further raises the neuroinflammation issue as evidence that "the art also acknowledges that many issues still need to be resolved in immunotherapy of AD in humans," such that undue experimentation would be required to practice the invention. Applicants believe that neuroinflammation is irrelevant to the issue of enablement. Neuroinflammation has been found to be occur in clinical trials involving an active immunization approach, which differs from the passive inflammation approach of the presently described invention. To date there is no evidence of neuroinflammation in clinical trials involving a passive immunization approach and the Examiner has not set forth any reason to believe it will occur. Moreover, neuroinflammation is a potential adverse side effect that has no bearing on whether the claimed method is actually effective and enabled for its claimed purpose, the treatment of Alzheimer's disease as defined in the specification, i.e. obtaining beneficial or desired results including, without limitation, reducing amyloid plaques. Side effects are the FDA's concern, not the PTO's.

In attempting to establish that undue experimentation would be required to practice the presently claimed invention, the Examiner asserts that "both at the time of filing and now, effective therapy for the treatment and prevention of Alzheimer's has eluded researchers" (Office Action at 8). But the references cited fail to support this assertion. For example, De Lustig et al. (*Rev in Neurosciences*, 1994; 5:213-225) was published 13 years ago, and 9 years before the filing of the present application; it is thus not useful in establishing the state of the art at any time period relevant to this application. The Examiner states that Vickers (*Drugs Aging*, 2002, 19(7):487-494) "notes that there is no effective treatment currently available to reverse, slow down or prevent the course of Alzheimer's disease." However, Vickers actually *supports* Applicants' argument that no undue experimentation would be needed for the skilled artisan to practice the claimed invention. Vickers notes that "[o]ne of the main pathological features that characterizes AD is the formation of extracellular deposits of fibrils, termed 'plaques', which are principally composed of the ß-amyloid peptide" (*Id.* at

487), and suggests targeting such plaques (as Applicants' invention does) as an "advantageous" strategy for addressing the nerve cell degeneration underlying Alzheimer's disease:

> While current FDA-approved treatments for AD utilize amelioration of the cholinergic deficit, by the action of acetylcholinesterase inhibitors, this approach achieves only significant symptomatic relief in a subset of patients with AD and does not address the progressive underlying neuronal degeneration. Newer therapeutic strategies can be broadly classified into two groups....The first approach, sometimes referred to as the 'plaque-busting' strategy, either targets key stages of the amyloidegenic pathway and/or seeks to eliminate ß-amyloid deposits once they have established in the brain.

Id. at 489.

In summary, when reasonably interpreted in view of the knowledge in the art, and considering the high level of skill in the art, no undue experimentation is required to make or use the presently claimed invention. Accordingly, reconsideration and withdrawal of the §112, first paragraph rejection is respectfully requested.

Rejection Under 35 USC §§ 112, 2d paragraph

Claims 1,2, 4-14, 16-27, 29-38 and 51-53 stand rejected under 35 USC §112, 2d paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner alleges at page 10 of the Office Action that "'binds preferentially' in claims 1, 2, 13, 14, 26 and 27 is a relative term which renders the claim indefinite" and that "one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." The Examiner states that incorporation of the phrase "binds specifically" or "specifically binds" into the claims would negate this rejection.

Applicants do not agree that use of the term "binds preferentially" renders the claims indefinite, and notes that the specification at paragraph [0056] defines the terms "specifically binds" and "preferentially binds" and states that they are used interchangeably therein. Nonetheless, to expedite allowance of the present application, Applicants have amended the claims to replace "binds preferentially" with "specifically binds" in accordance with the Examiner's suggestion. Accordingly, reconsideration and withdrawal of the §112, second paragraph rejection is respectfully requested.

Rejections Under 35 USC §102

A. Claims 1, 2, 4-14, 16-27, 29-38, and 51-53 stand rejected under 35 USC §102(e) as being anticipated by US Patent Application Publication No. 2003/0073655 of Chain, "as evidenced by Zeitlin et al." (hereinafter "Chain").

Applicants respectfully traverse this rejection in view of the arguments presented below.

The claims as amended are directed to the use of an antibody that binds preferentially to amino acids 28-40 of $Aß_{1-40}$ peptide and does not show significant cross-reactivity with $Aß_{1-42}$ and $Aß_{1-43}$ peptide for treating Alzheimer's disease, suppressing the formation of amyloid plaques, or reducing amyloid plaques in a subject.

To anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Applicants respectfully submit that the disclosure of Chain does not teach or suggest each and every element of the present claims.

As acknowledged by the Examiner, Chain is silent with respect to the affinity of the monoclonal antibodies described therein. The Examiner tries to remedy this deficiency by making the conclusory statement, based on a second reference, that "monoclonal antibodies are recognized in the art as possessing high specificity and binding affinity, *typically* in the range of 10^{-8} to 10^{-10} M, as evidenced by Zeitlin et al." (Office Action at 12-13; emphasis added). As noted in MPEP §2131, the use of a second reference to establish anticipation is improper: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a *single* prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added).

The Examiner appears to be using Zeitlin to argue that the affinity limitations of claims 4-7, 16-19, and 29-32 are an inherent property of the Chain antibodies. Even using the principle of inherency, Chain does not anticipate these claims. Although a reference may still anticipate if a particular element not expressly disclosed in the reference is inherent in its disclosure, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robinson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Co. v.*

Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991)). The Court further states that "[i]nherency, however, may not be established by probabilities or possibilities," and "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* In the present application, the Examiner has not established, by merely citing a reference regarding "typical" binding affinities, that the Chain antibodies *necessarily* have the binding affinity of claims 4-7, 16-19, and 29-32.

The Examiner next asserts that "[a]s the recited binding limitations have been met, it would be an expected property of the disclosed monoclonal anti-Aß antibodies to competitively inhibit the binding of other monoclonal antibodies" (Office Action at 13) such that the limitations of claims 8, 9, 20, 21, 33, and 34 are met by Chain. As previously discussed, the binding limitations have *not* been met by Chain, and the Examiner's attempt to remedy this by relying on a second reference and an allegedly "typical" quality of antibodies is improper and insufficient. Even if the recited binding limitations had in fact been met by Chain, no explanation as to why competitive inhibition of the binding of other monoclonal antibodies would be an "expected" property of the Chain antibodies is provided.

Accordingly, Chain does not anticipate claims 1, 2, 4-14, 16-27, 29-38, and 51-53 of the present application. Reconsideration and withdrawal of this §102 rejection are respectfully requested.

B. Claims 1, 2, 4-14, 16-27, 29-38, and 51-53 stand rejected under 35 USC §102(e) as being anticipated by US Patent Application Publication No. 2004/0241164 of Bales et al. (hereinafter "Bales").

Applicants respectfully traverse this rejection in view of the arguments presented below.

As provided above, to anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Applicants respectfully submit that the disclosure of Bales does not teach or suggest each and every element of the present claims.

Bales is directed to an anti-Aß antibody having an affinity for Aß greater than 10^{-9} M, that preferably recognizes the same epitope that antibody 266 recognizes or competes with antibody 266 for binding with soluble Aß. Antibody 266 recognizes epitopes between amino acids 13 and 28 of Aß (see paragraph [0005]), not between amino acids 28 and 40 as in the presently claimed invention. Moreover, the presently claimed antibodies require that there be no significant cross-reactivity with Aß$_{1-42}$ and Aß$_{1-43}$ peptide. Bales neither teaches nor suggests a preference for antibodies without such cross-reactivity; in fact most of the antibodies disclosed by Bales (and all of the ones shown to have a higher affinity for soluble Aß and thus to "more quickly and more significantly effect improvement in cognitive function in conditions and diseases involving Aß") are shown therein to bind Aß$_{1-42}$.

The Examiner points to monoclonal antibody 2G3, described in Bales as recognizing Aß$_{1-40}$ and not Aß$_{1-42}$, and extrapolates from this description that "logic would dictate that the epitope for these antibodies would reside in the C-terminus of Aß, and would comprise residues 28-40 of Aß, and more particularly, would include amino acids 39 and/or 40 of the Aß1-40 peptide" and that it would be an "expected property of the disclosed high affinity monoclonal anti-Aß1-40 antibodies to competitively inhibit the binding of other monoclonal antibodies" (Office Action at 14). Nowhere in Bales is any of these properties actually disclosed, and references to expected properties and the dictates of logic is not sufficient to establish inherent anticipation, as required by *In re Robinson* and *Continental Can Co.,* discussed *supra*.

Moreover, Bales does not provide an enabling disclosure of 2G3. The description of 2G3 is limited to the fact that it recognizes Aß$_{1-40}$ and not Aß$_{1-42}$. The amino acid sequence of the antibody is not provided, nor is there a description for a method of making it. No evidence is provided that 2G3 would be effective for the treatment of Alzheimer's disease or any symptoms thereof, even in mice, let alone humans. A claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research,* 346 F.3d 1051, 1054 (Fed. Cir. 2003).

Accordingly, Bales does not anticipate claims 1, 2, 4-14, 16-27, 29-38, and 51-53 of the present application. Reconsideration and withdrawal of this §102 rejection are respectfully requested.

CONCLUSION

Applicants respectfully submit that the application as amended is in condition for allowance, and early, favorable action is respectfully requested. In the event that there are any questions relating to this Amendment or to the application in general, the

Examiner is requested to telephone the undersigned concerning such questions so that the prosecution of this application can be expedited.

Respectfully submitted,

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